PHOTOPOLYMERIZABLE BIODEGRADABLE HYDROGELS AS TISSUE CONTACTING MATERIALS AND CONTROLLED-RELEASE CARRIERS

BACKGROUND OF THE INVENTION

This is a divisional of application U.S. Ser. No. 08/022,687 filed in the U.S. Patent & Trademark Office on Mar. 1, 1993, now U.S. Pat. No. 5,410,016 entitled 'Photopolymerizable Biodegradable Hydrogels as Tissue Contacting Materials and Controlled-Release Carriers' which is a continuation-in-part of U.S. patent application No. 07/843,485, filed Feb. 28, 1992, now abandoned entitled "Photopolymerizable Biodegradable Hydrogels as Tissue Contacting Materials and Controlled Release Carriers" by Jeffrey A. Hubbell, Chandrashekhar P. Pathak, and Amarpreet S. Sawhney.

FIELD OF THE INVENTION

The present invention relates to photopolymerizable biodegradable hydrogels for use as tissue adhesives and in controlled drug delivery.

Hydrogels as controlled-release carriers

Biodegradable hydrogels can be carriers for biologically active materials such as hormones, enzymes, antibiotics, antineoplastic agents, and cell suspensions. Temporary preservation of functional properties of a carried species, as well as controlled release of the species into local tissues or systemic circulation, are possible. Proper choice of hydrogel macromers can produce membranes with a range of permeability, pore sizes and degradation rates suitable for a variety of applications in surgery, medical diagnosis and treatment.

Adhesives and sealers

Fibrin gels have been used extensively in Europe as sealants and adhesives in surgery (Thompson et al., 1988, "Fibrin Glue: A review of its preparation, efficacy, and adverse effects as a topical hemostat," *Drug Intell. and Clin. Pharm.,* 22: 946; Gibble et al., 1990, (1990), "Fibrin glue: the perfect operative sealant?" *Transfusion,* 30(8): 741). However, they have not been used extensively in the United States due to concerns relating to disease transmission from blood products. Synthetic polymers have been explored as adhesives (Lipatova, 1986, "Medical polymer adhesives," *Advances in Polymer Science* 79: 65–93), but these materials have been associated with local inflammation, cytotoxicity, and poor biocompatibility.

Prevention of postoperative adhesions.

Formation of post-surgical adhesions involving organs of the peritoneal cavity and the peritoneal wall is a frequent and undesirable result of abdominal surgery. Surgical trauma to the tissue caused by handling and drying results in release of a serosanguinous (proteinaceous) exudate which tends to collect in the pelvic cavity (Holtz, G., 1984). If the exudate is not absorbed or lysed within this period it becomes ingrown with fibroblasts, and subsequent collagen deposition leads to adhesion formation.

Numerous approaches to elimination of adhesion formation have been attempted, with limited success in most cases. Approaches have included lavage of the peritoneal cavity, administration of pharmacological agents, and the application of barriers to mechanically separate tissues. For example, Boyers et al., (1988) "Reduction of postoperative pelvic adhesions in the rabbit with Gore-Tex surgical membrane," *Fertil. Steril.,* 49: 1066, examined Gore-Tex surgical membranes in the prevention of adhesions. For a review of adhesion prevention, see Holtz (1984) "Prevention and management of peritoneal adhesions," *Fertil. Steril.,* 41: 497–507. However, none of these approaches has been cost effective and effective in in vivo studies.

Solutions of Poloxamer 407 have been used for the treatment of adhesions, with some success. Poloxamer is a copolymer of ethylene oxide and propylene oxide and is soluble in water; the solutions are liquids at room temperature. Steinleitner et al. (1991) "Poloxamer 407 as an Intraperitoneal Barrier Material for the Prevention of Postsurgical Adhesion Formation and Reformation in Rodent Models for Reproductive Surgery," *Obstetrics and Gynecology,* 77(1):48 and Leach et al. (1990) "Reduction of postoperative adhesions in the rat uterine horn model with poloxamer 407, *Am. J. Obstet. Gynecol.,* 162(5): 1317, examined Poloxamer solutions in peritoneal adhesion models and observed statistically significant reductions in adhesions; however, they were unable to eliminate adhesions, perhaps because of limited adhesion and retention on the injury site.

Oxidized regenerated cellulose has been used extensively to prevent adhesions and is an approved clinical product, trade-named Interceed TC7. This barrier material has been shown to be somewhat effective in rabbits (Linsky et al., 1987 "Adhesion reduction in a rabbit uterine horn model using TC-7," *J. Reprod. Med.,* 32: 17; Diamond et al., 1987 "Pathogenesis of adhesions formation/reformation: applications to reproductive surgery," Microsurgery, 8: 103) and in humans (Interceed (TC7) *Adhesion Barrier Study Group,* 1989). It was shown to be more effective if pretreated with heparin, but was still unable to completely eliminate adhesions (Diamond et al., 1991 "Synergistic effects of INTERCEED(TC7) and heparin in reducing adhesion formation in the rabbit uterine horn model," *Fertility and Sterility,* 55(2): 389).

In summary, several lavage/drug/material approaches have been explored, but none of these approaches has been able to eliminate adhesions. An ideal material barrier would not evoke an adhesion response itself, stay in place without suturing (Holtz et al., 1982 "Adhesion induction by suture of varying tissue reactivity and caliber," *Int. J. Fert.,* 27: 134), degrade over a few weeks' time, effectively reduce adhesions to very low extent, and be capable of delivering a drug to the local site of application for several days' time. None of the approaches developed and described to date meet these requirements.

Synthetic biodegradable polymers

The field of biodegradable polymers has developed rapidly since the synthesis and biodegradability of polylactic acid was first reported by Kulkarni et al., 1966 "Polylactic acid for surgical implants," *Arch. Surg.,* 93: 839. Several other polymers are known to biodegrade, including polyanhydrides and polyorthoesters, which take advantage of labile backbone linkages, as reported by Domb et al., 1989 *Macromolecules,* 22: 3200; Heller et al., 1990 *Biodegradable Polymers as Drug Delivery Systems,* Chasin, M. and Langer, R., Eds., Dekker, New York, 121–161. Since it is desirable to have polymers that degrade into naturally occurring materials, polyaminoacids have been synthesized, as reported by Miyake et al., 1974, for in vivo use. This was the basis for using polyesters (Holland et al., 1986 Controlled Release, 4: 155–180) of α-hydroxy acids (viz., lactic acid, glycolic acid), which remain the most widely used biodegradable materials for applications ranging from closure devices (sutures and staples) to drug delivery systems (U.S. Pat. No. 4,741,337 to Smith et al.; Spilizewski et al., 1985